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(54) Title: METERED DOSE INHALER FOR BECLOMETHASONE DIPROPIONATE

(57) Abstract

A metered dose inhaler having part or all of its internal surfaces coated with one or more fluorocarbon polymers, optionally in combination with one or more non-fluorocarbon polymers, for dispensing an inhalation drug formulation comprising beclomethasone dipropionate or a physiologically acceptable solvate thereof, and a fluorocarbon propellant, optionally in combination with one or more other pharmacologically active agents or one or more excipients.

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METERED DOSE INHALER FOR BECLOMETHASONE DIPROPIONATE

BACKGROUND OF THE INVENTION

Drugs for treating respiratory and nasal disorders are frequently administered in aerosol formulations through the mouth or nose. One widely used method for dispensing such aerosol drug formulations involves making a suspension formulation of the drug as a finely divided powder in a liquefied gas known as a propellant. The suspension is stored in a sealed container capable of withstanding the pressure required to maintain the propellant as a liquid. The suspension is dispersed by activation of a dose metering valve affixed to the container.

A metering valve may be designed to consistently release a fixed, predetermined mass of the drug formulation upon each activation. As the suspension is forced from the container through the dose metering valve by the high vapor pressure of the propellant, the propellant rapidly vaporizes leaving a fast moving cloud of very fine particles of the drug formulation. This cloud of particles is directed into the nose or mouth of the patient by a channelling device such as a cylinder or open ended cone. Concurrently with the activation of the aerosol dose metering valve, the patient inhales the drug particles into the lungs or nasal cavity. Systems of dispensing drugs in this way are known as "metered dose inhalers" (MDI's). See Peter Byron, *Respiratory Drug Delivery*, CRC Press, Boca Raton, FL (1990) for a general background on this form of therapy.

Patients often rely on medication delivered by MDI's for rapid treatment of respiratory disorders which are debilitating and in some cases, even life threatening. Therefore, it is essential that the prescribed dose of aerosol medication delivered to the patient consistently meet the specifications claimed by the manufacturer and comply with the requirements of the FDA and other

regulatory authorities. That is, every dose in the can must be the same within close tolerances.

Some aerosol drugs tend to adhere to the inner surfaces, i.e., walls of the can, valves, and caps, of the MDI. This can lead to the patient getting significantly less than the prescribed amount of drug upon each activation of the MDI. The problem is particularly acute with hydrofluoroalkane (also known as simply "fluorocarbon" propellant systems, e.g., P134a and P227, under development in recent years to replace chlorofluorocarbons such as P11, P114, and P12.

We have found that coating the interior can surfaces of MDI's with a fluorocarbon polymer significantly reduces or essentially eliminates the problem of drug adhesion or deposition on the can walls and thus ensures consistent delivery of medication in aerosol form from the MDI.

SUMMARY OF THE INVENTION

A metered dose inhaler having part or all of its internal metallic surfaces coated with one or more fluorocarbon polymers, optionally in combination with one or more non-fluorocarbon polymers, for dispensing an inhalation drug formulation comprising beclomethasone dipropionate or a physiologically acceptable solvate thereof, and a fluorocarbon propellant, optionally in combination with one or more other pharmacologically active agents or one or more excipients.

DETAILED DESCRIPTION OF THE INVENTION

The term "metered dose inhaler" or "MDI" means a unit comprising a can, a crimped cap covering the mouth of the can, and a drug metering valve situated in the cap , while the term "MDI system" also includes a suitable channelling device. The terms "MDI can" means the container without the cap and valve. The term "drug metering valve" or "MDI valve" refers to a valve and its associated mechanisms which delivers a predetermined amount of drug formulation from an MDI upon each activation. The channelling device may

comprise, for example, an actuating device for the valve and a cylindrical or cone-like passage through which medicament may be delivered from the filled MDI can via the MDI valve to the nose or mouth of a patient, e.g. a mouthpiece actuator. The relation of the parts of a typical MDI is illustrated in US Patent 5,261,538 incorporated herein by reference.

U.S. Patent No.3,312,590, incorporated herein by reference, teaches an antiinflammatory steroid compound know by the chemical name 9-chloro-1 1D, 17, 21-trihydroxy-16fi-methylprergna-1,4-diene-3, 20-dione 17, 21-dipropionate and the generic name "beclomethasone dipropionate". Beclomethasone dipropionate in aerosol form, has been accepted by the medical community as useful in the treatment of asthma and is marketed under the trademarks "Beclovent", "Becotide", and "Beconase".

The term "drug formulation" means beclomethasone dipropionate (or a physiologically acceptable solvate thereof) optionally in combination with one or more other pharmacologically active agents such as other antiinflammatory agents, analgesic agents or other respiratory drugs and optionally containing one or more excipients. The term "excipients" as used herein mean chemical agents having little or no pharmacological activity (for the quantities used) but which enhance the drug formulation or the performance of the MDI system. For example, excipients include but are not limited to surfactants, preservatives, flavorings, antioxidants, antiaggregating agents, and cosolvents, e.g., ethanol and diethyl ether.

Suitable surfactants are generally known in the art, for example, those surfactants disclosed in European Patent Application No. 0327777. The amount of surfactant employed is desirable in the range of 0.0001% to 50% weight to weight ratio relative to the drug, in particular, 0.05 to 5% weight to weight ratio. A particularly useful- surfactant is 1,2-di[7-(F-hexyl) hexanoyl]-glycero-3-phospho-N,N,N-trimethylethanolamine also know as 3, 5, 9-trioxa-4-phosphadocosan-1-aminium, 17, 17, 18,18,19, 19, 20, 20, 21, 21, 22, 22, 22-tridecafluoro-7-[(8, 8, 9, 9,10, 10, 11, 11, 12, 12, 13, 13, 13-tridecafluoro-1-oxotridecyl)oxy]-4-hydroxy-N, N, N-trimethyl-10-oxo-, inner salt,.4-oxide.

A polar cosolvent such as C_{2-6} aliphatic alcohols and polyols eg ethanol, isopropanol and propylene glycol, and preferably ethanol, may be included in the drug formulation in the desired amount, either as the only excipient or in addition to other excipients such as surfactants. Suitably, the drug formulation may contain 0.01 to 5% w/w based on the propellant of a polar cosolvent eg ethanol, preferably 0.1 to 5% w/w e.g. 0.1 to 1% w/w.

It will be appreciated by those skilled in the art that the drug formulation for use in the invention may, if desired, contain beclomethasone dipropionate (or a physiologically acceptable solvate thereof) in combination with one or more other pharmacologically active agents. Such medicaments may be selected from any suitable drug useful in inhalation therapy. Appropriate medicaments may thus be selected from, for example, analgesics, e.g. codeine, dihydromorphine, ergotamine, fentanyl or morphine; anginal preparations, e.g. diltiazem; antiallergics, e.g. cromoglycate, ketotifen or nedocromil; antiinfectives e.g. cephalosporins, penicillins, streptomycin, sulphonamides, tetracyclines and pentamidine; antihistamines, e.g. methapyrilene; anti-inflammatories, e.g. fluticasone (e.g. the propionate), flunisolide, budesonide, tipredane or triamcinolone acetonide; antitussives, e.g. noscapine; bronchodilators, e.g. salbutamol, salmeterol, ephedrine, adrenaline, fenoterol, formoterol, isoprenaline, metaproterenol, phenylephrine, phenylpropanolamine, pirbuterol, reproterol, rimiterol, terbutaline, isoetharine, tulobuterol, orciprenaline, or (-)-4-amino-3,5-dichloro- α -[[[6-[2-(2-pyridinyl)ethoxy]hexyl]amino]methyl]benzenemethanol; diuretics, e.g. amiloride; anticholinergics e.g. ipratropium, atropine or oxitropium; hormones, e.g. cortisone, hydrocortisone or prednisolone; xanthines e.g. aminophylline, choline theophyllinate, lysine theophyllinate or theophylline; and therapeutic proteins and peptides, e.g. insulin or glucagon. It will be clear to a person skilled in the art that, where appropriate, the medicaments may be used in the form of salts (e.g. as alkali metal or amine salts or as acid addition salts) or as esters (e.g. lower alkyl esters) or as solvates (e.g. hydrates) to optimise the activity and/or stability of the medicament and/or to minimise the solubility of the medicament in the propellant.

Particularly preferred drug formulations contain beclomethasone dipropionate (or a physiologically acceptable solvate thereof) in combination with a bronchodilator such as salbutamol (e.g. as the free base or the sulphate salt) or salmeterol (e.g. as the xinafoate salt).

"Propellants" used herein mean pharmacologically inert liquids with boiling points from about room temperature (25°C) to about -25°C which singly or in combination exert a high vapor pressure at room temperature. Upon activation of the MDI system, the high vapor pressure of the propellant in the MDI forces a metered amount of drug formulation out through the metering valve then the propellant very rapidly vaporizes dispersing the drug particles. The propellants used in the present invention are low boiling fluorocarbons; in particular, 1,1,1,2-tetrafluoroethane also known as "propellant 134a" or "P134a" and 1,1,1,2,3,3,3-heptafluoropropane also know as "propellant 227" or "P 227".

Drug formulations for use in the invention may be free or substantially free of formulation excipients e.g. surfactants and cosolvents etc. Such drug formulations are advantageous since they may be substantially taste and odour free, less irritant and less toxic than excipient-containing formulations. Thus, a preferred drug formulation consists essentially of beclomethasone dipropionate (or a physiologically acceptable solvate thereof), optionally in combination with one or more other pharmacologically active agents particularly salbutamol (or a physiologically acceptable salt thereof), and a fluorocarbon propellant. Preferred propellants are 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoro-n-propane or mixtures thereof, and especially 1,1,1,2-tetrafluoroethane.

Most often the MDI can and cap are made of aluminum or an alloy of aluminum, although other metals not affected by the drug formulation, such as stainless steel, an alloy of copper, or tin plate, may be used. An MDI can may also be fabricated from glass or plastic. Preferably, however, the MDI cans employed in the present invention are made of aluminium or an alloy thereof. Advantageously, strengthened aluminium or aluminum alloy MDI cans may be employed. Such strengthened MDI cans are capable of withstanding particularly stressful coating and curing conditions, e.g. particularly high temperatures, which

may be required for certain fluorocarbon polymers. Strengthened MDI cans which have a reduced tendency to malform under high temperatures include MDI cans comprising side walls and a base of increased thickness and MDI cans comprising a substantially ellipsoidal base (which increases the angle between the side walls and the base of the can), rather than the hemispherical base of standard MDI cans. MDI cans having an ellipsoidal base offer the further advantage of facilitating the coating process.

The drug metering valve consists of parts usually made of stainless steel, a pharmacologically inert and propellant resistant polymer, such as acetal, polyamide (e.g., Nylon®), polycarbonate, polyester, fluorocarbon polymer (e.g., Teflon®) or a combination of these materials. Additionally, seals and "O" rings of various materials (e.g., nitrile rubbers, polyurethane, acetyl resin, fluorocarbon polymers), or other elastomeric materials are employed in and around the valve.

Fluorocarbon polymers for use in the invention include fluorocarbon polymers which are made of multiples of one or more of the following monomeric units: tetrafluoroethylene (PTFE), fluorinated ethylene propylene (FEP), perfluoroalkoxyalkane (PFA), ethylene tetrafluoroethylene (ETFE), vinyldienefluoride (PVDF), and chlorinated ethylene tetrafluoroethylene. Fluorinated polymers which have a relatively high ratio of fluorine to carbon, such as perfluorocarbon polymers e.g. PTFE, PFA, and FEP, are preferred.

The fluorinated polymer may be blended with non-fluorinated polymers such as polyamides, polyimides, polyethersulfones, polyphenylene sulfides and amine-formaldehyde thermosetting resins. These added polymers improve adhesion of the polymer coating to the can walls. Preferred polymer blends are PTFE/FEP/polyamideimide, PTFE/polyethersulphone (PES) and FEP-benzoguanamine.

Particularly preferred coatings are pure PFA, FEP and blends of PTFE and polyethersulphone (PES).

Fluorocarbon polymers are marketed under trademarks such as Teflon®, Tefzel®, Halar® , Hostaflon®, Polyflon® and Neoflon®. Grades of polymer include FEP DuPont 856-200, PFA DuPont 857-200, PTFE-PES DuPont 3200-100, PTFE-FEP-polyamideimide DuPont 856P23485, FEP powder DuPont 532 and PFA Hoechst 6900n. The coating thickness is in the range of about 1μm to about 1mm. Suitably the coating thickness is in the range of about 1μm to about 100μm, e.g. 1μm to 25μm. Coatings may be applied in one or more coats.

Preferably the fluorocarbon polymers for use in the invention are coated onto MDI cans made of metal, especially MDI cans made of aluminium or an alloy thereof.

The particle size of the particular (e.g., micronised) drug should be such as to permit inhalation of substantially all the drug into the lungs upon administration of the aerosol formulation and will thus be less than 100 microns, desirably less than microns, and, in particular, in the range of 1-10 microns, e.g., 1-5 microns.

The final aerosol formulation desirably contains 0.005-10% weight to weight ratio, in particular 0.005-5% weight to weight ratio, especially 0.01-1.0% weight to weight ratio, of drug relative to the total weight of the formulation.

A further aspect of the present invention is a metered dose inhaler having part or all of its internal metallic surfaces coated with one or more fluorocarbon polymers, optionally in combination with one or more fluorocarbon polymers, for dispersing an inhalation drug formulation comprising beclomethasone dipropionate and a fluorocarbon propellant optionally in combination with one or more other pharmacologically active agents and one or more excipients.

A particular formulation for use in the metered dose inhaler of the present invention comprises:

(a) beclomethasone dipropionate monohydrate, the particle size of substantially all the monohydrate being less than 20 microns;
(b) at least 0.015% by weight of the formulation of water in addition to the water of crystallization associated with said monohydrate; and
(c) a fluorocarbon propellant.

Such aerosol formulations desirably contain at least 0.015% (e.g., 0.015 to 0.1%) by weight of the formulation of water (excluding the water of crystallization associated with the beclomethasone dipropionate monohydrate), preferably at least 0.02%, for example 0.025% by weight or more of added water. Preferred formulations according to the invention contain at least 0.026%, for example 0.026 to 0.08% by weight of water, in addition to the water of crystallization associated with the beclomethasone dipropionate monohydrate. Optionally, a cosolvent such as ethanol may be included in the formulation in the desired amount. Suitably, the formulation may contain 0.05 to 3.0% w/w based on the propellant of a polar cosolvent such as ethanol. Preferably the fluorocarbon propellant is 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoro-n-propane or mixtures thereof, and especially 1,1,1,2-tetrafluoroethane.

Further drug formulations for use in the invention are free or substantially free of surfactants. Thus, a further formulation comprises or consists essentially of beclomethasone dipropionate or a physiologically acceptable solvate thereof, optionally in combination with one or more other pharmacologically active agents, a fluorocarbon propellant and 0.01 to 0.05% w/w based on the propellant of a polar cosolvent such as ethanol, which formulation is free of surfactant. Preferably the propellant is 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoro-n-propane, although mixtures thereof may also be used.

A particular aspect of the present invention is an MDI having part or essentially all of its internal surfaces e.g. metallic surfaces coated with PFA or FEP, or blended fluoropolymer resin systems such as PTFE-PES with or without a proper coat of polyamideimide or polyethersulfone for dispersing a drug formulation as defined hereinabove. Preferably the MDI can is made of aluminum or an alloy thereof.

The MDI can may be coated by the means known in the art of metal coating. For example, a metal, such as aluminum or stainless steel, may be precoated as coil stock and cured before being stamped or drawn into the can shape. This method is well is suited to high volume production for two reasons. First, the art of

coating coil stock is well developed and several manufacturers can custom coat metal coil stock to high standards of uniformity and in a wide range of thicknesses. Second, the precoated stock can be stamped or drawn at high speeds and precision by essentially the same methods used to draw or stamp uncoated stock.

Other techniques for obtaining coated cans is by electrostatic dry powder coating or by spraying preformed MDI cans inside with formulations of the coating fluorinated polymer/polymer blend and then curing. The preformed MDI cans may also be dipped in the fluorocarbon polymer/polymer blend coating formulation and cured, thus becoming coated on the inside and out. The fluorocarbon polymer/polymer blend formulation may also be poured inside the MDI cans then drained out leaving the insides with the polymer coat. Conveniently, for ease of manufacture, preformed MDI cans are spray-coated with the fluorinated polymer/polymer blend.

The fluorocarbon polymer/polymer blend may also be formed in situ at the can walls using plasma polymerization of the fluorocarbon monomers. Fluorocarbon polymer film may be blown inside the MDI cans to form bags. A variety of fluorocarbon polymers such as ETFE, FEP, and PTFE are available as film stock.

The appropriate curing temperature is dependent on the fluorocarbon polymer/polymer blend chosen for the coating and the coating method employed. However, for coil coating and spray coating temperatures in excess of the melting point of the polymer are typically required, for example, about 50° C above the melting point for up to about 20 minutes such as about 5 to 10 minutes eg about 8 minutes or as required. For the above named preferred and particularly preferred fluorocarbon polymer/polymer blends curing temperatures in the range of about 300°C to about 400°C, e.g. about 350°C to 380°C are suitable. For plasma polymerization typically temperatures in the range of about 20°C to about 100°C may be employed.

The fluorocarbon polymer may also be formed in situ at the can walls using plasma polymerization of the fluorocarbon monomers. Fluorocarbon polymer film

may be blown inside the MDI cans to form bags. A variety of fluorocarbon polymers such as ETFE, FEP, and PTFE are available as film stock.

The MDI's taught herein may be prepared by methods of the art (e.g., see Byron, above and U.S. patent 5,345,980) substituting conventional cans for those coated with a fluorinated polymer. That is, beclomethasone dipropionate and other components of the formulation are filled into an aerosol can coated with a fluorinated polymer. The can is fitted with a cap assembly which is crimped in place. The suspension of the drug in the fluorocarbon propellant in liquid form may be introduced through the metering valve as taught in U.S. 5,345,980 incorporated herein by reference.

The MDI's with fluorocarbon coated interiors taught herein may be used in medical practice in a similar manner as non-coated MDI's now in clinical use. However the MDI's taught herein are particularly useful for containing and dispensing inhaled drug formulations with hydrofluoroalkane fluorocarbon propellants such as 134a with little, or essentially no, excipient and which tend to deposit or cling to the interior walls and parts of the MDI system. In certain case it is advantageous to dispense an inhalation drug with essentially no excipient, e.g., where the patient may be allergic to an excipient or the drug reacts with an excipient.

MDI's containing the formulations described hereinabove, MDI systems and the use of such MDI systems for the treatment of respiratory disorders e.g. asthma comprise further aspects of the present invention.

It will be apparent to those skilled in the art that modifications to the invention described herein can readily be made without departing from the spirit of the invention. Protection is sought for all the subject matter described herein including any such modifications.

The following non-limitative Examples serve to illustrate the invention.

EXAMPLES

Example 1

Standard 12.5 mL MDI cans (Presspart Inc., Cary, NC) were spray-coated (Livingstone Coatings, Charlotte, NC) with primer (DuPont 851-204) and cured to the vendor's standard procedure, then further spray-coated with either FEP or PFA (DuPont 856-200 and 857-200, respectively) and cured according to the vendor's standard procedure. The thickness of the coating is approximately 10μm to 50μm. These cans are then purged of air (see PCT application number W094/22722 (PCT/EP94/00921)), the valves crimped in place, and a suspension of about 24 mg beclomethasone dipropionate in about 18 gm P134a is filled through the valve.

Example 2

Standard 0.46 mm thick aluminum sheet (United Aluminum) was spray-coated (DuPont, Wilmington, DE) with FEP (DuPont 856-200) and cured. This sheet was then deep-drawn into cans (Presspart Inc., Cary, NC). The thickness of the coating is approximately 10μm to 50μm. These cans are then purged of air, the valves crimped in place, and a suspension of about 60 mg beclomethasone dipropionate in about 18 gm P134A is filled through the valve.

Example 3

Standard 12.5 ml MDI cans (Presspart Inc., Cary NC) are spray-coated with PTFE-PES blend (DuPont) as a single coat and cured according to the vendor's standard procedure. The thickness of the coating is between approximately 1μm and approximately 20μm. These cans are then purged of air, the valves crimped in place, and a suspension of about 68mg micronised beclomethasone dipropionate monohydrate in about 6.1mg water and about 18.2g P134a is filled through the valve.

Example 4

Standard 12.5ml MDI cans (Presspart Inc., Cary NC) are spray-coated with PTFE-FEP-polyamideimide blend (DuPont) and cured according to the vendor's standard procedure. The thickness of the coating is between approximately 1μm and approximately 20μm. These cans are then purged of air the valves crimped in place, and a suspension of about 68mg micronised beclomethasone dipropionate monohydrate in about 6.1mg water and about 18.2g P134a is filled through the valve.

Example 5

Standard 12.5ml MDI cans (Presspart Inc., Cary NC) are spray-coated with FEP powder (DuPont FEP 532) using an electrostatic gun. The thickness of the coating is between approximately 1μm and approximately 20μm. These cans are then purged of air, the valves crimped in place, and a suspension of about 68mg micronised beclomethasone dipropionate monohydrate in about 6.1mg water and about 18.2g P134a is filled through the valve.

Example 6

Standard 0.46mm thick aluminium sheet is spray coated with FEP-Benzoguanamine and cured. This sheet is then deep-drawn into cans. These cans are then purged of air, the valves crimped in place, and a suspension of about 68mg micronised beclomethasone dipropionate monohydrate in about 6.1mg water and about 18.2g P134a is filled through the valve.

Example 7

Standard 12.5 ml MDI cans (Presspart Inc., Cary NC) are spray-coated with an aqueous dispersion of PFA (Hoechst PFA-6900n) and cured. The thickness of the coating is between approximately 1μm and approximately 20μm. These cans

are then purged of air, the valves crimped in place, and a suspension of about 68mg micronised beclomethasone dipropionate monohydrate in about 6.1mg water and about 18.2g P134a is filled through the valve.

Example 8

Standard 12.5 ml MDI cans (Presspart Inc., Cary NC) are spray-coated with PTFE-PES blend (DuPont) as a single coat and cured according to the vendor's standard procedure. The thickness of the coating is between approximately 1μm and approximately 20μm. These cans are then purged of air, the valves crimped in place, and about 68mg micronised beclomethasone dipropionate monohydrate in about 182mg ethanol and about 18.2g P134a is filled through the valve.

Example 9

Standard 12.5ml MDI cans (Presspart Inc., Cary NC) are spray-coated with PTFE-FEP-polyamideimide blend (DuPont) and cured according to the vendor's standard procedure. The thickness of the coating is between approximately 1μm and approximately 20μm. These cans are then purged of air the valves crimped in place, and about 68mg micronised beclomethasone dipropionate monohydrate in about 182mg ethanol and about 18.2g P134a is filled through the valve.

Example 10

Standard 12.5ml MDI cans (Presspart Inc., Cary NC) are spray-coated with FEP powder (DuPont FEP 532) using an electrostatic gun. The thickness of the coating is between approximately 1μm and approximately 20μm. These cans are then purged of air, the valves crimped in place, and about 68mg micronised beclomethasone dipropionate monohydrate in about 182mg ethanol and about 18.2g P134a is filled through the valve.

Example 11

Standard 0.46mm thick aluminium sheet is spray coated with FEP-Benzoguanamine and cured. This sheet is then deep-drawn into cans. These cans are then purged of air, the valves crimped in place, and about 68mg micronised beclomethasone dipropionate monohydrate in about 182mg ethanol and about 18.2g P134a is filled through the valve.

Example 12

Standard 12.5 ml MDI cans (Presspart Inc., Cary NC) are spray-coated with an aqueous dispersion of PFA (Hoechst PFA-6900n) and cured. The thickness of the coating is between approximately 1µm and approximately 20µm. These cans are then purged of air, the valves crimped in place, and about 68mg micronised beclomethasone dipropionate monohydrate in about 182mg ethanol and about 18.2g P134a is filled through the valve.

Example 13

Standard 12.5 ml MDI cans (Presspart Inc., Cary NC) are spray-coated with PTFE-PES blend (DuPont) as a single coat and cured according to the vendor's standard procedure. The thickness of the coating is between approximately 1µm and approximately 20µm. These cans are then purged of air, the valves crimped in place, and about 13.6mg micronised beclomethasone dipropionate in about 107mg ethanol and about 21.4g P227 is filled through the valve.

Example 14

Standard 12.5ml MDI cans (Presspart Inc., Cary NC) are spray-coated with PTFE-FEP-polyamideimide blend (DuPont) and cured according to the vendor's standard procedure. The thickness of the coating is between approximately 1µm and approximately 20µm. These cans are then purged of air the valves crimped in place, and about 13.6mg micronised beclomethasone dipropionate in about 107mg ethanol and about 21.4g P227 is filled through the valve.

Example 15

Standard 12.5ml MDI cans (Presspart Inc., Cary NC) are spray-coated with FEP powder (DuPont FEP 532) using an electrostatic gun. The thickness of the coating is between approximately 1μm and approximately 20μm. These cans are then purged of air, the valves crimped in place, and about 13.6mg micronised beclomethasone dipropionate in about 107mg ethanol and about 21.4g P227 is filled through the valve.

Example 16

Standard 0.46mm thick aluminium sheet is spray coated with FEP-Benzoguanamine and cured. This sheet is then deep-drawn into cans. These cans are then purged of air, the valves crimped in place, and about 13.6mg micronised beclomethasone dipropionate in about 107mg ethanol and about 21.4g P227 is filled through the valve.

Example 17

Standard 12.5 ml MDI cans (Presspart Inc., Cary NC) are spray-coated with an aqueous dispersion of PFA (Hoechst PFA-6900n) and cured. The thickness of the coating is between approximately 1μm and approximately 20μm. These cans are then purged of air, the valves crimped in place, and about 13.6mg micronised beclomethasone dipropionate in about 107mg ethanol and about 21.4g P227 is filled through the valve.

Examples 18-22

Examples 3 to 7 are repeated except that about 24mg salbutamol as the free base or equivalent weight of salt e.g. sulphate with about 12mg beclomethasone dipropionate monohydrate in about 364mg ethanol and about 18.2g P134a is filled through the valve.

Examples 23-42

Examples 3 to 22 are repeated except that modified 12.5ml MDI cans having a substantially ellipsoidal base (Presspart Inc., Cary NC) are used.

Dose delivery from the MDIs tested under simulated use conditions is found to be constant, compared to control MDIs filled into uncoated cans which exhibit a significant decrease in dose delivered through use.

We claim:

1. A metered dose inhaler having part or all of its internal surfaces coated with one or more fluorocarbon polymers, optionally in combination with one or more non-fluorocarbon polymers, for dispensing an inhalation drug formulation comprising beclomethasone dipropionate or a physiologically acceptable solvate thereof, and a fluorocarbon propellant, optionally in combination with one or more other pharmacologically active agents or one or more excipients.

2. An inhaler according to Claim 1 containing said drug formulation.

3. An inhaler according to Claim 2 wherein said drug formulation further comprises a surfactant.

4. An inhaler according to Claim 2 or Claim 3 wherein said drug formulation further comprises a polar cosolvent.

5. An inhaler according to claim 2 wherein said drug formulation comprises 0.01 to 5 % w/w based on the weight of propellant of a polar cosolvent, which formulation is substantially free of surfactant.

6. An inhaler according to Claim 4 or Claim 5, wherein the polar cosolvent is ethanol.

7. An inhaler according to any one of Claims 2 to 6, wherein said drug formulation comprises beclomethasone dipropionate or a physiologically acceptable solvate thereof in combination with salmeterol or salbutamol or a physiologically acceptable salt thereof.

8. An inhaler according to Claim 2, wherein said drug formulation comprises
   (a) beclomethasone dipropionate monohydrate, the particle size of substantially all the monohydrate being less than 20 microns;
   (b) at least 0.15% by weight of the formulation of water in addition to the water of crystallisation associated with the monohydrate; and

(c) a fluorocarbon propellant.

9. An inhaler according to Claim 8, wherein the formulation further comprises 0.05 to 3% w/w based on the propellant of a polar cosolvent.

10. An inhaler according to Claim 9, wherein the polar cosolvent is ethanol.

11. An inhaler according to Claim 2, wherein said drug formulation consists essentially of beclomethasone dipropionate or a physiologically acceptable solvate thereof, optionally in combination with one or more other pharmacologically active agents, a fluorocarbon propellant and 0.01 to 5 % w/w based on the propellant of a polar cosolvent, which formulation is substantially free of surfactant.

12. An inhaler according to any one of Claims 2 to 11, wherein the fluorocarbon propellant is 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoro-n-propane or mixtures thereof.

13. An inhaler according to Claim 12, wherein the fluorocarbon propellant is 1,1,1,2-tetrafluoroethane.

14. An inhaler according to any one of claims 1 to 13 comprising a can made of metal wherein part or all of the internal metallic surfaces are coated.

15. An inhaler according to Claim 14 wherein the metal is aluminium or an alloy thereof.

16. An inhaler according to any one of Claims 1 to 15, wherein said fluorocarbon polymer is a perfluorocarbon polymer.

17. An inhaler according to Claim 16 wherein said fluorocarbon polymer is selected from PTFE, PFA, FEP and mixtures thereof.

18. An inhaler according to any one of Claims 1 to 17, wherein said fluorocarbon polymer is in combination with a non-fluorocarbon polymer selected from polyamideimide and polyethersulphone.

19. An inhaler according to any one of Claims 1 to 18 comprising a substantially ellipsoidal base.

20. A metered dose inhaler system comprising a metered dose inhaler according to any one of Claim 1 to 19 fitted into suitable channelling device for oral or nasal inhalation of the drug formulation.

21. Use of a metered dose inhaler system according to Claim 20 for the treatment of respiratory disorders.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 96/05009

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 B65D83/14 A61K9/00 A61M15/00 B05D5/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 B65D A61K A61M B05D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 642 992 (CIBA-GEIGY AG) 15 March 1995 see column 2, line 18-32 see column 3, line 1-20 see column 3, line 27 - column 6, line 9	1,14-17, 20
Y	see column 3 - column 4; claims 2,5,6	2-13
X	US,A,5 176 132 (DROUGHT NICHOLAS A M ET AL) 5 January 1993 see column 3, line 16-21 see column 1, line 58 - column 2, line 3	1,16,17, 20
Y	US,A,5 202 110 (DALBY RICHARD N ET AL) 13 April 1993 see column 2, line 22-26 see claim 11	2,12,13

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 June 1996	31.07.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Bichlmayer, K-P

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 96/05009

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO,A,93 11743 (GLAXO GROUP LTD) 24 June 1993 see page 4, line 18-21 see page 5, line 19-26 see page 7, line 27 - page 8, line 2 see page 8, line 21-28 see examples 12,14 see claims 19,20	2,7
Y	WO,A,92 08446 (GLAXO GROUP LTD) 29 May 1992 see page 2, line 6-13 see page 3 - page 5, paragraph 1 see claims 1-3,5,7,10	3,4,6,11
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A	WO,A,81 01375 (GLYCO METALL WERKE ;STERNISA D (DE); SCHNEIDER W (DE); HODES E (DE) 28 May 1981 see page 3, line 20-26 see page 4, line 11-18 see page 5, line 12-17	18

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 96/05009

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/05009

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 21
because they relate to subject matter not required to be searched by this Authority, namely:
Method of treatment of the human or animal body by therapy.
See Rule 39.1(iv) PCT.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 96/05009

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